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The Structure of Futoquinol, a Constituent of *Piper futokadzura* Sieb. et Zucc.

Shuji Takahashi and Akira Ogiso

Central Research Laboratories, Sankyo Co., Ltd. [1]

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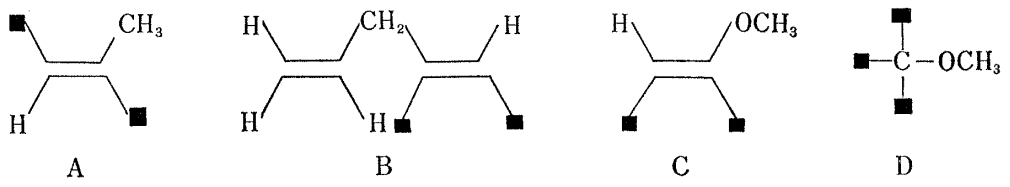
Futoquinol, isolated from *Piper futokadzura* Sieb. et Zucc., has been characterized as a novel quinol–ether compound. The structure has been determined by means of 100 Mc NMR and chemical data of futoquinol and its derivatives obtained by dienone–phenol rearrangement.

From *Piper futokadzura* Sieb. et Zucc., we have isolated four new crystalline components designated futoenone,[2] futoamide,[3] futoxide (crotepoxide)[4] and futoquinol.[5] As principles of the fragrant odor of this plants, α-pinene, camphene, β-pinene, sabinene and isoasarone have been detected. This paper deals with the details of our studies on futoquinol (I).

Futoquinol, $C_{21}H_{22}O_5$, mp 97—98°, exhibits signals in the nuclear magnetic resonance (NMR) spectrum at 5.92 ppm attributable to methylene protons (2H) adjacent to oxygen and at 6.7—7.0 ppm assignable to three aromatic protons. The infrared (IR) spectrum of futoquinol shows absorption bands at 1665 and 1635 cm^{-1}. The ultraviolet (UV) absorption (260 and 295 mμ) is a characteristic curve consisting of the overlapping of a 3,4-methylenedioxystyrene and an α,β-unsaturated carbonyl chromophore.



■ indicates a carbon bearing no proton.

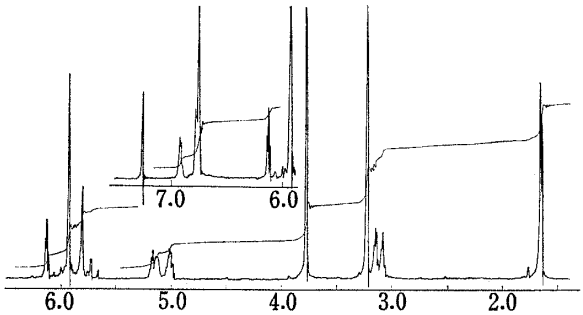


Fig. 1. NMR Spectrum of Futoquinol

1) Location: *2–58, Hiromachi 1–chome, Shinagawa–ku, Tokyo.*
2) A. Ogiso, M. Kurabayashi, H. Mishima, and M.C. Woods, *Tetrahedron Letters*, **1968**, 2003; M.C. Woods, I. Miura, A. Ogiso, M. Kurabayashi, and H. Mishima, *ibid.*, **1968**, 2009.
3) S. Takahashi, M. Kurabayashi, A. Ogiso, and H. Mishima, *Chem. Pharm. Bull.* (Tokyo), **17**, 1225 (1969).
4) S. Takahashi, *Phytochemistry*, **8**, 321 (1969); S.M. Kupchan, R.J. Hemingway, P. Coggaon, A.T. McPhail, and G.A. Sim, *J. Am. Chem. Soc.*, **90**, 2982 (1968).
5) See reference 4 for the isolation.

From decoupling experiments with futoquinol were deduced the partial structure shown in Fig. 1, (A), (B), and (C). The splitting of the signal (doublet, J=1.0 cps) at 1.68 ppm due to an allylic methyl protons is caused by coupling with the *trans*–olefinic proton at 6.92 ppm. The absence of a nuclear Overhauser effect (NOE, see Fig. 3) with the olefinic proton when the methyl protons are irradiated, provided evidence for the partial structure (A). Irradiation of the allylic methylene protons centered at 3.12 ppm affected the signals due to olefinic protons at 5.07, 5.09, 5.86 and 6.13 ppm shown in Fig. 2. Observation of NOE with the olefinic proton at 6.13 ppm, which was effected by the irradiation of the methylene protons, suggested the sequence of these protons as illustrated in structure (B). The IR absorption band at 890 cm^{-1} is also in accord with the presence of a terminal methylene group. Two signals due to methoxyl groups appear at 3.27 and 3.78 ppm. The former, an aliphatic methoxyl, is attached to a tertiary carbon as in structure (D), since no other signal is found in the 3.5—5.0 ppm region except those of the methoxyl groups. The latter is assignable to an olefinic methoxyl group. The partial sturcture (C) was suggested by the marked increase of the integration curve for the olefinic proton singlet at 5.81 ppm on irradiation of the methoxyl group.

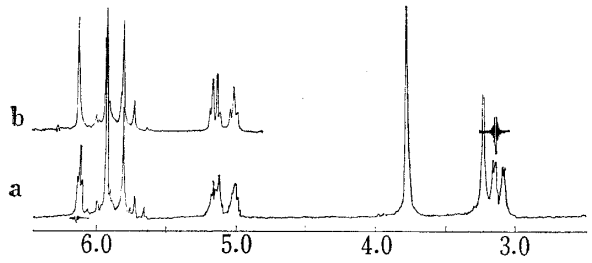


Fig. 2. Decoupling of Futoquinol

a: Normal
b: Irr. of Methylene Protons at 3.12 ppm

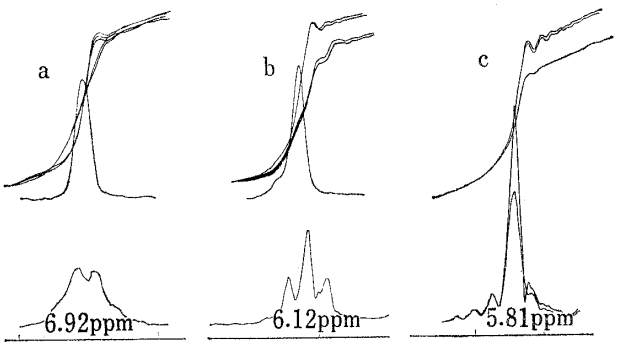


Fig. 3. NOE of Olefinic Protons of Futoquinol

a: Irr. of CH_3 at 1.68 ppm
b: Irr. of CH_2 at 3.12 ppm
c: Irr. of OCH_3 at 3.78 ppm

Reduction of futoquinol with sodium borohydride gave an epimeric mixture of alcohols (II), which was oxidized with manganese dioxide regenerating futoquinol. The NMR of one epimeric alcohol was assigned to establish the partial structure (E) shown in Fig. 4. The doublet at 4.49 ppm due to the proton attached to the carbinol group was changed to a singlet when the olefinic proton at 5.08 ppm was irradiated.

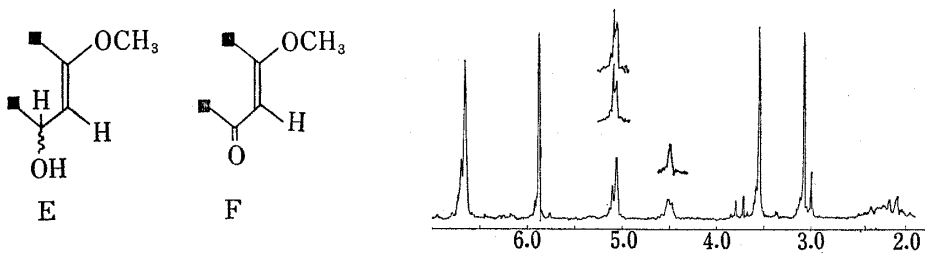


Fig. 4. Decoupling of Epimeric Alcohol (II)

Thus, the partial structure (C) for futoquinol can be expanded to (F) having an α,β-unsaturated ketone in agreement with the UV and IR data. Partial structures (A), (B), (D), and (F) together with a 3,4-methylenedioxyphenyl group account for all twenty–two hydrogens, all five oxygens and twenty–one carbons present in the futoquinol molecule ($C_{21}H_{22}O_5$). Connecting these parts leads to the structure of futoquinol having a quinol–ether character.

The 2,5-cyclohexadienone system was determined by dienone–phenol rearrangement of futoquinol and its derivatives. Treatment of futoquinol with sulfuric acid in acetic anhydride

furnished the acetate (III), $C_{23}H_{24}O_6$, mp 95—96°. In the NMR shown in Fig. 5, one of the methoxyl signals of futoquinol shifts to lower field at 3.78 ppm, and the two olefinic protons disappear, while an aromatic proton singlet at 6.63 ppm appears. In addition, the spectral data, an absorption band at 1760 cm^{-1} in the IR and the NMR signal at 2.27 ppm due to acetyl group as well as the UV maximum at 267 mμ, indicate that the quinol ether system of futoquinol is converted into a stilbene structure. Since it is known that quinol ethers react like ordinary alkyl cyclohexadienone with the alkoxy group remaining intact and the geminal alkyl group migrating,[6] the structure of the rearranged product must be illustrated as III. Although, 1,3-allyl migration in a dienonephenol rearrangement has been reported.[7] In the case of futoquinol, the possibility of the 1,3-rearrangement can be excluded by the structure of the epimeric alcohol (II) (*vide supra*).

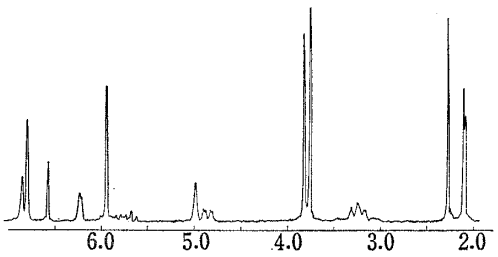


Fig. 5. NMR Spectrum of Acetate (III)

Dihydrofutoquinol (IV), mp 86—88°, prepared by hydrogenation of futoquinol, reacted under the same acidic conditions to furnish the dihydroacetate, mp 56—59° with spectra consistent with structure V.

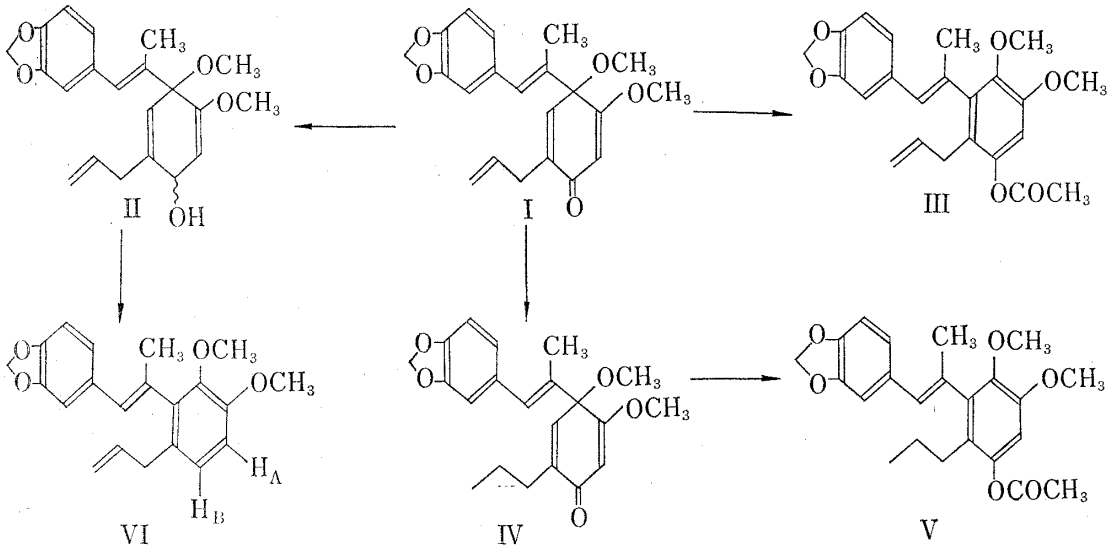
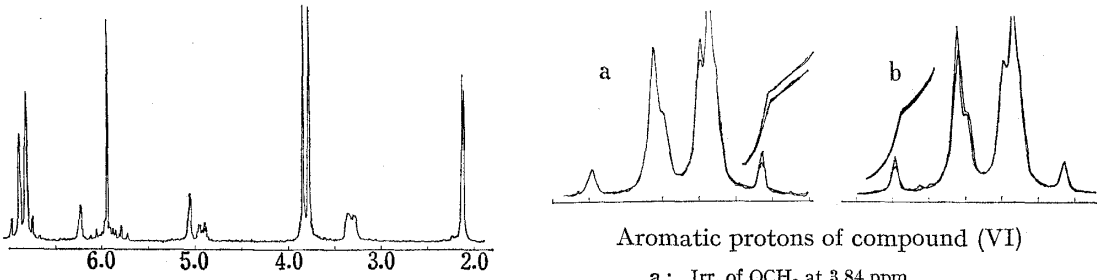


Chart 1

The mixture of epimeric alcohols (II) underwent rearrangement with hydrochloric acid in methanol to give a homogeneous compound (VI). From the NMR spectrum (Fig. 6) of this compound may be deduced the aromatic ring substituents as the structure (VI). The coupling constant (J=7.5 cps) for the two aromatic protons at 6.78 and 6.93 ppm is in accord with that of ortho protons. One of the protons exhibits long-range coupling with the allylic methylene protons, the other reveals a NOE when the methoxyl signal (3.84 ppm) is irradiated. Since it is clear that H_B of the aromatic ring is the proton produced by dienol-benzene rearrangement, the hydroxyl group of the epimeric alcohols (II) is attached to the position of H_B. Namely, futoquinol itself has the carbonyl function at the same position.

The position of the olefinic methyl group in futoquinol was confirmed by the following results. Generally, the signal of an α-olefinic proton relative to a phenyl group shows a charac-

6) A.J. Waring, "Cyclohexadienone" in "Advances in Alicyclic Chemistry," Vol. 1, ed. by H. Hart and G.J. Karabatsos, 1966, p. 129.
7) B. Miller, *J. Am. Chem. Soc.*, **87**, 5115 (1965).



NMR spectrum of Compound (VI)

Aromatic protons of compound (VI)

a: Irr. of OCH_3 at 3.84 ppm
b: Irr. of Allylic CH_2 at 3.33 ppm

Fig. 6

teristic shift to lower field in the NMR. The chemical shifts of olefinic protons referring to the series of methysticin and the congeners[8] show good agreement with that of futoquinol at 6.29 ppm. The mass spectrum of futoquinol provides evidence for the position of the olefinic methyl group. The elimination of an acetylene group from the fragment ion at *m/e* 161 [22% of base peak at *m/e* 313 (M^+–C_3H_7)] formed by the initial cleavage of the molecule as indicated on Chart. 2, leads to the fragment peak at *m/e* 135 (30%). This fragmentation and relative abundance can take place only in the case that the olefinic methyl group is located at a β-position from the phenyl group and not α.

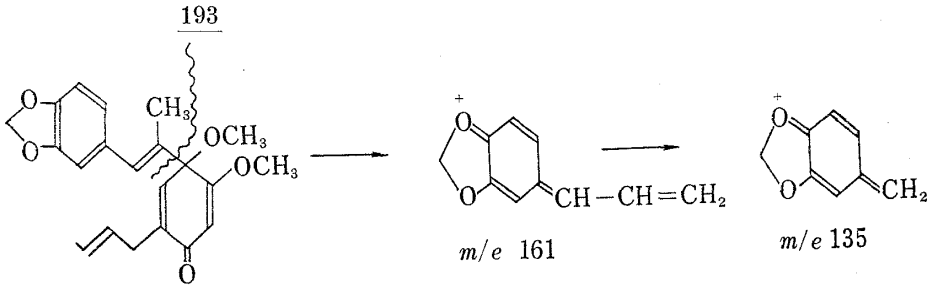


Chart 2

Experimental[9]

Futoquinol (I)——Crude material isolated from the leaves and stems of *Piper futokadzura* Sieb. et Zucc.[4] was recrystallized from methanol to give colorless prisms, mp 97—98°. *Anal.* Calcd. for $C_{21}H_{22}O_5$: C, 71.17; H, 6.25. Found: C, 70.92; H, 6.37. UV λ_{max} mμ (ε): 260 (16700), 295 (10760). IR ν_{max} cm^{-1}: 1665, 1635, 1605, 1505, 1490, 890. Mass Spectrum *m/e*: 354 (M^+), 313 (base peak), 285, 282, 194, 178, 162, 135, 103.

Sodium Borohydride Reduction of Futoquinol——A solution of 500 mg of futoquinol and 100 mg of sodium borohydride in 15 ml of ethanol was allowed to stand overnight at room temperature. Excess borohydride was decomposed by addition of small amount of acetic acid, and work-up as usual gave 500 mg of an oily product. Thin-layer chromatography (TLC) on silica gel showed that this oil was an epimeric mixture of the alcohols (II). The separation of the epimers was effected by careful chromatography on neutral alumina eluting with benzene followed by benzene–ether.

Oxidation of Epimeric Alcohols (II)——A mixture of 100 mg of the epimeric mixture of the alcohols (II) and 1.0 g of manganese dioxide in 10 ml of chloroform was stirred vigorously for 1 hr at room temperature. After filtration, the solution was evaporated to give crystalline residue which was recrystallized from methanol to give 70 mg of prisms, mp 97—98°. This compound was identical with futoquinol in all respects; *i.e.*, TLC, UV, IR and mixed melting point.

Rearrangement of Futoquinol——To a solution of 200 mg of futoquinol in 1 ml of acetic anhydride was added one drop of conc. sulfuric acid under ice-cooling. After standing for 1 hr at 0°, the reaction mixture was poured into ice-water and extracted with ether. The residual oil obtained by evaporation of the solvent

8) P. Beak and H. Abelson, *J. Org. Chem.*, 27, 3715 (1962).
9) The melting points were determined in capillary tubes and uncorrected. The ultraviolet absorption spectra were measured in 95% ethanol using a Beckman DK-2A spectrometer. Infrared spectra were determined in nujol on an Infracord spectrometer. The NMR spectra were determined with a Varian HA-100 spectrometer using tetramethylsilane as an internal reference in deuterochloroform.

was chromatographed on silica gel (7.0 g) affording a solid which was recrystallized from *n*-hexane–ether yielding 150 mg of prisms, mp 95—96°. *Anal.* Calcd. for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10. Found: C, 69.69; H, 6.12. UV λ_{max} mμ (ε): 267 (14000). IR ν_{max} cm^{-1}: 1760, 1640, 1605, 1505, 1485, 1220, 900.

Hydrogenation of Futoquinol——A solution of 1.0 g of futoquinol in 30 ml of ethanol was hydrogenated over 30 mg of Adams' catalyst under atmospheric pressure at room temperature. One mole equivalent of hydrogen was taken up and absorption ceased. After removal of the catalyst, the filtrate was evaporated to give dihydrofutoquinol (IV), which was recrystallized from *n*-hexane–ether to give prisms, mp 86—87°. *Anal.* Calcd. for $C_{21}H_{24}O_5$: C, 70.76; H, 6.67. Found: C, 70.75; H, 6.67. IR ν_{max} cm^{-1}: 1660, 1630, 1605, 1500, 1490.

Rearrangement of Dihydrofutoquinol (IV)——To a solution of 2.0 g of dihydrofutoquinol (IV) in 10 ml of acetic anhydride was added one drop of conc. sulfuric acid under ice–cooling. The resulting purple solution was allowed to stand for 15 min at 0° and poured into ice–water. Extraction with ether, washing the extract with water and subsequent evaporation of the solvent gave an oil. The oil was chromatographed on silica gel (60 g) and eluted with benzene to give a crystalline mass which was recrystallized from *n*-hexane–ether to yield 1.3 g of prisms, mp 57—59°. *Anal.* Calcd. for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58. Found: C, 69.50; H, 6.65. UV λ_{max} mμ (ε): 267 (13500). IR ν_{max} cm^{-1}: 1770, 1605, 1505, 1490, 1220.

Rearrangement of Epimeric Alcohols (II)——To a solution of 750 mg of the mixture of epimeric alcohols (II) in 5 ml of methanol was added few drops of 35% hydrochloric acid under ice–cooling. After standing for 30 min at room temperature, the reaction mixture was poured into aqueous sodium bicarbonate solution. Extraction with ether and evaporation of the extract gave an oil which showed single spot on TLC. Purification of the product was carried out by column chromatography on silica gel (15 g) using benzene as the eluent. IR ν_{max} cm^{-1}: 1640, 1600, 1505, 1490, 890.

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